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Letter to the Editor

The "bottom-up" approach does not necessarily bound low-dose risk

Starr and Swenberg (2013) proposed a "bottom-up" modeling approach, the purpose of which is to bound low-dose cancer risks from exogenous exposure to chemicals that are found endogenously within the body and thus provide a reality check on risk estimates derived from traditional approaches used by Agencies such as the Environmental Protection Agency (EPA). The approach does not use tumor incidence data from laboratory animals or humans exposed at different doses for quantification, but relies only on the endogenous concentration level, C_0, of an internal metric in a specific tissue (e.g., N^2-hydroxymethyl-dG monoadducts in several tissues, in the case of formaldehyde) and the background risk, P_0, for the cancer type of interest. The ratio P_0/C_0 is used to estimate the slope of the dose–response relationship between risk and the internal dose at low (exogenous) exposures, and an upper bound on this ratio is described as an "upper bound" on the dose–response slope at low (exogenous) exposures by virtue of the following procedures inherent in the approach: (1) for purposes of bounding, all of the background risk is assumed to be due to the endogenous internal dose (as measured, for example, by the endogenous adduct concentration), (2) the dose–response relationship for risk as a function of endogenous adduct concentration is assumed to be linear, and (3) a lower confidence limit, C_{0L}, on the estimate of the endogenous concentration, C_0, is used.

The purpose of this letter is to articulate why the proposed "bottom-up" approach does not necessarily "bound" low-dose risk. We demonstrate a fundamental point, that P_0/C_{0L} is not necessarily an upper bound on the slope of the dose–response relationship at low (exogenous) exposures.

Fig. 1 depicts the "bottom-up" approach graphically. The figure shows that the approach could underestimate the dose–response slope at C_0 if the dose–response curve is concave upwards in the endogenous range. The dotted line with slope P_0/C_0 is the central estimate of the linear slope used in the "bottom-up" approach to represent the risk at low exogenous exposures. The heavy solid curve in Fig. 1 represents a plausible dose–response relationship (which, of course, is unobservable near and below C_0). It is clear from this figure that whenever the true dose–response relationship is upward-curving in the endogenous concentration range, the linear assumption used in the "bottom-up" approach is not conservative in estimating slope or risk for nonzero exogenous exposures. Likewise, the upper bound on P_0/C_0 obtained by the use of the lower bound on C_0 is not necessarily an upper bound on the low-dose slope of the true dose–response relationship. The authors of the "bottom-up" approach have not provided a basis to conclude that using the lower confidence limit on C_0 or other "conservative assumptions" will necessarily overcome any underestimation of the slope at C_0 resulting from the linear assumption. Other assumptions might overcome this underestimation in particular cases, but from the procedure per se, one cannot know when that would, or would not, occur.

Starr and Swenberg (2013) did not contend that the endogenous dose–response relationship was not upward-curving, but instead they assume tacitly that a linear dose–response relationship over the endogenous range bounded the slope of all possible endogenous dose–response relationships. However, as illustrated, when a dose–response relationship is curved upwards over endogenous concentrations, assuming a linear dose–response relationship over the endogenous range will result in an underestimation of the slope at C_0. A sublinear dose–response relationship over the endogenous range is clearly plausible on biological grounds. For example, it is likely that baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work most effectively for lower levels of endogenous adducts.

The authors note that their approach is consistent with the concept of additivity to background disease processes (Crump et al., 1976) and that P_0/C_{0L} is directly comparable to the estimate derived from the linearized multistage model. However, adherence to this concept of additivity does not require the globally linear constraint (i.e., linear all the way down to an origin at zero endogenous dose) imposed by the "bottom-up" approach but instead only requires local linearity in the proximity of zero exogenous dose.

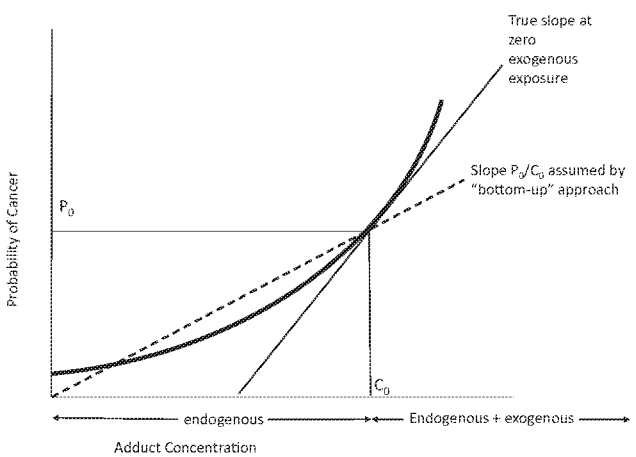

Fig. 1. Graphical representation of the "bottom-up" approach in a case in which the true dose–response relationship curves upward in the (unobservable) endogenous range.

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